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SCIENTIFIC EDITORIAL

The future of left atrial appendage occlusions: When extraordinary claims require evidence...



Le futur de l'exclusion de l'auricule gauche, besoin d'études pour aller plus loin

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Received 21 September 2015; received in revised form 29 September 2015;
accepted 29 September 2015
Available online 17 November 2015

KEYWORDS

Left atrial
appendage;
Watchman;
ACP;
Amulet;
Anticoagulation;
Atrial fibrillation

Atrial fibrillation (AF), the most common cardiac arrhythmia, is complex to manage because it is associated with many other morbid conditions and complications. The most severe complication of AF is ischaemic stroke, the third most frequent cause of death and the leading cause of serious disability worldwide. AF is one of the main causes of ischaemic stroke, being responsible for one in five cases [1].

Owing to the incidence and severity of ischaemic stroke, its prophylaxis is a crucial component of AF management. Stroke risk assessment scores such as the CHADS₂ [2] and the CHA₂DS₂-VASc [3] scores have been developed to assess the risk of thromboembolic events and to determine whether a patient with AF should receive anticoagulation. If the CHA₂DS₂-VASc score is 2 or more, then oral anticoagulation is firmly recommended. Some patients with a score of 1 should also receive anticoagulation, but this is recommended on an individual basis [4].

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MOTS CLÉS

Fermeture de
l'auricule gauche ;
Watchman ;
ACP ;
Amulet ;
Fibrillation
auriculaire

Despite the proven efficacy of anticoagulation with both warfarin and recently available non-vitamin K oral anticoagulants (NOACs), there is much reluctance to start patients on anticoagulation for fear of bleeding complications. Epidemiological studies have shown that more than one-third of patients with AF who are eligible for anticoagulation (CHA₂DS₂-VASc score ≥ 2) continue to be managed suboptimally with no anticoagulation or with only antiplatelet agents, presumably because of an overinflated perception of their risk of bleeding [5].

It is estimated that 90% of all cardiac clots that form during AF are localized to the left atrial appendage (LAA) [6]. As a result, LAA surgical ligation or mechanical occlusion has emerged since 1930 as a potential alternative to oral anticoagulation (OAC) to reduce the risk of AF-related stroke without a concomitant increase in bleeding risk [7]. In 2005, two entirely catheter-based devices, the Amplatzer Cardiac Plug (ACP) and the second-generation AMULET device (St Jude Medical), were approved in Europe. In March 2015, the US Food and Drug Administration (FDA) agency finally approved the Watchman left atrial appendage closure (LAAC) device (Boston Scientific) for the US market, after multiple reviews by FDA committees, starting in 2010. The aim of this device is to reduce the risk of LAA-mediated thromboembolism in patients who are not candidates for chronic anticoagulation.

The most comprehensive and long-term evaluation of the Watchman LAAC device was published by Holmes et al. [8]. This patient-level meta-analysis of the PROTECT AF [9] and the PREVAIL [10] randomized controlled trials and their respective registries, CAP and CAP2 [11], includes data on 1877 patients treated with the Watchman device and 382 control patients treated with long-term warfarin, totalling 5931 patient-years of follow-up. These data demonstrated that the LAAC device provides similar benefits to warfarin for reducing the composite efficacy endpoint of stroke, systemic embolism or cardiovascular death. However, on detailed analysis, ischaemic strokes were more frequent in the device group (1.6 vs. 0.9 events per 100 patient-years; hazard ratio 1.95; $P=0.05$), whereas haemorrhagic strokes occurred less frequently in the device group (0.15 vs. 0.22 events per 100 patient-years; hazard ratio 0.22; $P=0.004$). The authors also found a 52% reduction in cardiovascular death in patients treated with the Watchman device compared with warfarin (1.1 vs. 2.3 events per 100 patient-years; $P=0.006$).

Even if the conclusion of this meta-analysis [8] is encouraging, presenting the LAAC technique as safe, effective and preferable to chronic OAC therapy, OAC and NOACs remain the first-line therapy for thromboembolic prophylaxis in non-valvular AF. The LAAC device should not yet be considered

as superior treatment because randomized data are currently limited to only two studies with the Watchman device [9,10] comparing it only to a single agent (warfarin), and the ACP/AMULET data are based exclusively on observational studies. It is uncertain, for example, how the LAAC device will perform when compared with NOACs.

The European Heart Rhythm Association (EHRA)/European Association of Percutaneous Cardiovascular Interventions (EAPCI) [12] expert consensus statement on catheter-based LAA occlusion and, more recently, the expert consensus statement established by the Rhythm and Cardiac Pacing and the Atheroma and Interventional Cardiology Groups (GACI) of the French Society of Cardiology [13], recommend that OAC currently remains the standard of therapy for eligible patients. They defined patients with high thromboembolic risk (CHA₂DS₂-VASc score ≥ 2) and a chronic contraindication for anticoagulation as possible candidates for LAAC, while the French Health Authority (Haute Autorité de santé) recommends LAAC only for patients with very high thromboembolic risk (CHA₂DS₂-VASc score ≥ 4) with a formal contraindication for oral anticoagulation. Even though these restrictions on patient selection seem to be the most currently accepted clinical indication for LAA occlusion, no randomized data targeting this specific group of patients are yet available. On further analysis, we can conclude that the European statements and FDA approval are actually based solely on expert consensus because the only randomized controlled trials available (PROTECT AF and PREVAIL [9,10]) excluded patients ineligible for oral anticoagulation: *in fine* the specific population defined in the statement. An important point of these statements is the procedural environment. The EAPCI recommends that in the case of severe complications, the maximum transfer time to a cardiac surgery facility must be no longer than 60 minutes. In contrast, the statement edited by the two groups of the French Society of Cardiology [13] and the advice issued by the French Health Authority both underline the need for centres to offer heart surgery backup at the cathlab site, to manage catastrophic cardiac tamponades and device embolization, if necessary. At this stage of development of the technique, these restrictions appear to be a call for common sense and restraint. One-hour transportation in these difficult clinical conditions would probably prove fatal to patients. Currently, all efforts should be made to not unnecessarily increase patient risk. If, in the next few years, all implant centres gain full experience and if the procedural risk appears more acceptable and the patient indications extended, this position could be revised.

A crucial element of these recommendations is to determine which patients are eligible for LAAC (i.e. patients with a chronic contraindication for anticoagulation). As an example, intracranial haemorrhage (ICH) is the most frequent contraindication for anticoagulation in patients with AF, representing about 60% of contraindicated patients [14]. ICH is the second most common subtype of stroke and accounts for approximately 20% of all strokes, thus ICH patients may represent a large population potentially eligible for LAAC. However, it is important to establish which of these patients have a chronic and formal contraindication for anticoagulation. Among ICHs, lobar ICHs have a high risk of recurrence because they are associated with cerebral amyloid angiopathy, an incurable neurodegenerative disease, whereas deep ICHs are mostly induced by chronic hypertension, so blood pressure control can reduce their risk of recurrence. For these reasons, North American guidelines recommend avoidance of long-term anticoagulation after warfarin-associated spontaneous lobar ICH, while anticoagulation after deep ICH might be considered [15]. In the future, we may anticipate that patients with lobar ICH would be eligible for LAAC, whereas NOACs versus LAAC should be discussed for patients with deep ICH. This kind of discussion about ICH patients should be also performed for gastrointestinal bleedings, haematological disorders and geriatric patients in order to define the right population for LAAC.

Another important and pragmatic issue is the post-procedural management of antithrombotic therapy in patients ineligible for oral anticoagulation. Indeed, in the PROTECT AF and PREVAIL trials, contraindication for warfarin was an exclusion criterion and all Watchman-implanted patients were required to take warfarin for at least 45 days after implantation. Just a small, non-randomized trial (Aspirin Plavix Registry) reported the Watchman experience in 150 patients who were not eligible for long-term anticoagulation, demonstrating a reasonable safety profile over short-term follow-up [16]. Even these patients, however, were treated with 6 months of dual antiplatelet therapy followed by lifelong aspirin. However, dual antiplatelet therapy increases haemorrhagic risk and recently has been associated with severe ICH after device implantation [17,18]. A large clinical trial has also demonstrated twice as frequent major bleeding with dual antiplatelet therapy than with aspirin alone, especially for intracranial bleeding (0.4% vs. 0.2% per year, respectively; relative risk 1.87; 95% confidence interval 1.19–2.94; $P=0.006$) [16]. The absence of consensus concerning appropriate antithrombotic regimens after implantation in very high bleeding risk patients such as ICH patients should lead to well-designed registries and a randomized study to establish the post-procedural optimal strategy.

In conclusion, we believe that while LAAC appears promising, the scarcity of randomized data combined with issues regarding patient eligibility definitions in the only randomized trials currently undertaken should temper any overenthusiasm for LAAC. Although LAAC appears to be safe, effective and preferable to chronic OAC therapy for thromboembolic prophylaxis in non-valvular AF, the current indications should be limited to patients with AF who are at a very high risk of stroke and have clear contraindications for any form of anticoagulation. The place of NOACs in this treatment strategy remains to be updated, when

the data on NOACs in patients with previous ICH become available [19]. Single antiplatelet therapy with aspirin during device endothelialization, followed (or not) by lifelong aspirin, depending on the patient's vascular risk, might be considered for patients with a formal contraindication for OAC and in the absence of randomized controlled trial data.

Disclosure of interest

Pauline Renou declares that she has no competing interest.

Financial disclosures: Jean-Benoît Thambo is a proctor for St Jude medical and Boston Scientific.

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